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Biochemistry of Intestinal Development

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In biochemical terms, the rat small intestine is relatively immature at birth and for the first two postnatal weeks. Then during the third week a dramatic array of enzymic changes begins, and by the end of the fourth week the intestine has the digestive and absorptive properties of the adult. Selective examples of these changes are discussed with emphasis on their implications for toxicological studies. The review also includes a detailed consideration of the roles of the dietary change of weaning and of glucocorticoid and thyroid hormones in the regulation of intestinal development.

My aim in this paper is to use the rat as a model system for a discussion of the postnatal development of small intestinal function. Factors which affect the developmental process will be reviewed in terms of their implications for toxicological studies.

Morphologic Development of the Intestine

By the time of birth, the intestinal mucosa of the rat displays a high level of structural development characterized by villi lined with a single layer of columnar epithelial cells which have well-defined microvilli at their absorptive surface (*1-3*). After birth, continuous proliferation of epithelial cells occurs only in the lower regions of the crypts (*4, 5*), and cells migrate from there onto and along the villi, eventually being extruded from the tips into the lumen of the intestine. In adult rats and mice the generation time for the crypt cells is 10-14 hr (*6*), and the transit time along the length of the villus is approximately 48 hr (*7*). The characteristics of proliferation and migration of enterocytes in adult animals are dealt with in detail in the review by Lipkin (*8*). In neonatal rats, generation and migration of the cells is much slower than in adults. Despite the fact that the neonatal villi are shorter, the transit time is at least 96 hr (*7, 9*). During the third postnatal week there are significant changes in both cell kinetics and morphology leading to the more rapid proliferation and the longer villi and crypts that are characteristic of the adult animal (*9*).

In both neonatal and adult animals, the crypt-villus unit is a classical example of a system wherein proliferation precedes differentiation. The epithelial cells of the villus have many specialized enzymatic functions concerned with the precesses of digestion and absorption (*10, 11*). In contrast, the progenitor cells of the crypt have none of these specialized activities, but, as would be expected of proliferating tissue, they contain high activities of various enzymes involved in the synthesis of DNA (*12, 13*). Many of the specialized functions of the villus cells are associated with the luminal surface, i.e., with the microvilli.

The continuous renewal of the intestinal epithelium adds a degree of complexity to developmental studies with this organ. When dealing with the development of most other organs, one considers the change with time of the enzymatic properties of a stable population of cells. For example, in rat liver, the same cells that have high activity of ATP-citrate lyase and low activity of tryptophan oxygenase at birth, have these enzymatic patterns reversed by the time of weaning (*14*). In contrast, in the intestine, there are two ways in which enzyme patterns can be changed: by changes in a given population of enterocytes within their brief life-span and by simple replacement of one type of cell by another type from the proliferating pool. In a later section, evidence will be presented that it is the latter mechanism which is operative in the ontogenic changes that occur during the third week of life.

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Biochemical Development of the Intestine

Biochemically, the rat intestine is relatively immature at birth and for the first two postnatal weeks, then during the third and fourth weeks undergoes a dramatic array of functional changes. It is convenient to discuss the changes in two broad categories.

Activities Which Are High at Birth, Then Decline

One of the most striking features of the neonatal rat intestine is its ability to absorb intact macromolecules, including proteins (*15-17*), by the process of pinocytosis (*18-20*). The capacity for pinocytosis appears in the rat intestine by day 19 or 20 of intrauterine life (*21, 22*), remains high during the first two weeks of suckling, and then decreases markedly towards the end of the third week (*18, 19, 23*). Correspondingly, the proteolytic enzymes from the stomach and the pancreas which are low during the first two weeks of extrauterine life, increase significantly during the weaning period (*19, 24, 25*).

The absence of the adult mode of luminal digestion of protein in the neonatal rat and the presence of pinocytic capacity provides an explanation for the absorption of intact immunoglobulins during the suckling period (*16, 26*). On the other hand, since the developmental pattern of pinocytosis correlates with that for certain lysosomal enzymes (*23, 27*), it has been suggested (*23*) that the process of pinocytosis allows intracellular digestion of macromolecules during the period in which the mechanisms for extracellular digestion have not yet matured. This is not consistent with pinocytosis being important for the transfer of passive immunity to the newborn unless immunoglobulins are selectively protected from the action of lysosomal hydrolases. Various models to explain such selectivity have been proposed (*28-30*), and recent evidence (*31*) supports one of these models (*29*), namely that immunoglobulins are absorbed predominantly in the jejunum where lysosomal activity is low, whereas other proteins are absorbed and digested in the ileum where lysosomal activity is high.

Two points of relevance to toxicology are illustrated here. First, for both the adult intestine and the infant intestine, one should always remain open to the possibility that different regions may have quite different biochemical characteristics. Second, during the developmental period, proteins (and any ligands which may be bound to them) have direct access to intestinal epithelial cells as a result of pinocytosis.

In terms of digestive capacity, the neonatal rat intestine has hydrolytic activities which are specific for, and restricted to, the components of maternal milk. This is demonstrated very nicely by a consideration of carbohydrate digestion. Milk is relatively low in total carbohydrates, and the carbohydrates present are those not generally found in adult diets. The major carbohydrate in the milk of most placental mammals is lactose (*32*), and high activities of its disaccharidase, lactase, are found in the intestinal mucosa of the suckling animals (*33-35*). In the rat, lactase is detectable on day 18 of gestation, has maximal activity during the first week after birth, and then begins to decline, reaching adult values by the end of the fourth week (*36*). Many other species, including the human, have lower lactase activity in the adult than the newborn (*34*), and accordingly, show an inability to utilize ingested lactose in the postweaning period (*35*).

While lactose is the major carbohydrate received by the suckling mammal, the milks of various species are also known to contain sialic acid. Very interestingly, the digestive enzyme for this component, namely neuraminidase, has recently been found to have an ontogenic profile very similar to that of lactase (*37*).

Activities Which Are Absent or Low at Birth, Then Appear and/or Increase

Various disaccharidases (maltase, isomaltase, sucrase, and trehalase) fall into this category and thus their developmental patterns are in direct contrast to that of lactase. Maltase has low activity during the first two postnatal weeks then undergoes a 5- to 10-fold increase during the next two weeks (*38, 39*). For sucrase, isomaltase, and trehalase, the transition is even more sudden. These enzymes cannot be detected in the intestine during the first and second postnatal week, but their activities appear on approximately day 16 and rise rapidly, reaching adult levels by the end of the fourth week (*38-40*). These developmental changes in the nature of the disaccharidase activities of the intestine clearly have physiological significance in allowing the young animal to make the dietary change from lactose as the major carbohydrate during suckling, to maltose, isomaltose and sucrose as the major disaccharides after weaning (*41*). The temporal relationship between the developmental rise of sucrase activity and the process of weaning can be seen in Figure 1. The possibility of a casual relationship between these two phenomena is discussed in a later section.

In addition to the disaccharidases, there are various other hydrolytic enzymes of the intestine which

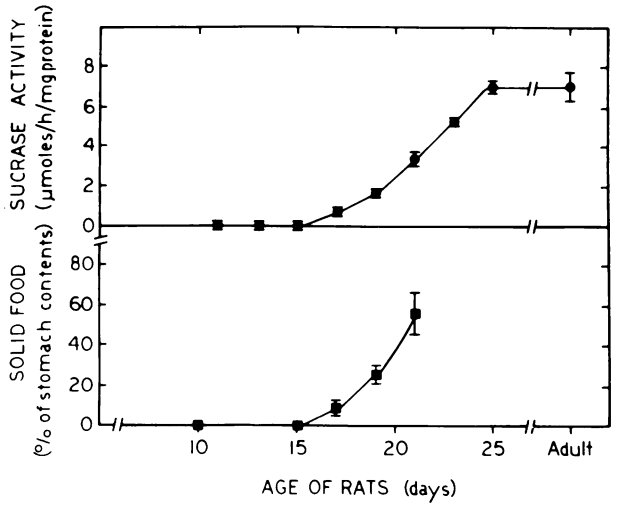

FIGURE 1. (Top) Activity of jejunal sucrase during postnatal development. Values are given as means ± SEM (n = 5). (Bottom) Pattern of weaning as indicated by the amount of chow in stomach contents at various ages. Values were obtained by dissecting the chow away from coagulated milk, weighing each component, then expressing the wt of chow as a % of the wt of milk plus chow. Values are given as means ± SEM (n = 5).

show distinct developmental patterns. Many workers have measured the marked increase in duodenal alkaline phosphatase activity which occurs during the third week of life in rats and mice (*34*). Much of the pioneer work by Moog on the development of intestinal function was accomplished with this enzyme (*42, 43*). The function of alkaline phosphatase in the intestine is not understood, although its distribution along the crypt-villus unit (*11*), and its localization in the microvilli of enterocytes (*44-46*) are suggestive of some role in digestion or absorption. Peptidases of the rat and mouse intestine also show marked increases during the third week of life (*43, 47*).

Regulation of Intestinal Development

Role of Diet

The possibility of dietary influence over the regulation of intestinal development is an obvious one considering the temporal correlation between the major enzymic changes in the intestine and the onset of weaning (Fig. 1). In terms of nutrition, weaning represents a transition from a high-fat, low-carbohydrate diet, and from a diet whose sole disaccharide is lactose to one in which the major disaccharides are sucrose and maltose. It is clear, however, that this dietary change cannot be considered the primary cause of the various enzymic and morphologic changes that occur in the intestine during the third postnatal week. We have shown (Fig. 2) that when weaning is prevented, the appearance of sucrase activity in the jejunum is not delayed. Conversely, oral administration of sucrose to 12-day-old rats has no effect on the developmental pattern for sucrase (*39*). If sucrose is administrated by gastrostomy to suckling rats, precocious increase of sucrase is observed; however, since this does not occur if the animals have been previously adrenalectomized, it is probably a stress response, rather than a dietary response (*41*). The same comment applies to the precocious appearance of sucrase, maltase and alkaline phosphatase following early weaning (*49*). Prolonged suckling does not delay the usual decrease in the capacity of the neonatal rat intestine to transport intact antibodies (*50*), and it delays, but does not prevent, the usual decline of lactase activity (*51*).

Given then, that the intestinal changes of the third week are initiated by some factor other than the dietary change of weaning (probably glucocorticoids, see below), there still remains the question of whether the dietary change modulates the extent or the timing of the ontogenic events. The case of sucrase development is particularly interesting. Figure 2 shows that although the timing of the appearance of jejunal sucrase is not affected by prevention of weaning, the activity at which the enzyme plateaus (days 25 and 27) is approximately half that seen in control (weaned) animals. Since in adult rats, jejunal sucrase activity is known to be affected by the sucrose and maltose content of the diet (*52, 53*) we have proposed that this effect of weaning prevention represents acquisition of the adult mode of enzymic regulation.

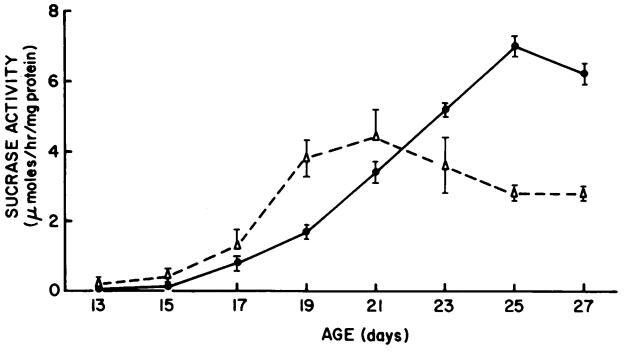

FIGURE 2. Effect of weaning-prevention on sucrase development for (●) four control litters raised in the regular manner and (Δ) four experimental litters raised on a schedule which prevented weaning. One pup from each litter was removed for sucrase assay every second day from days 13-27 inclusive. Results are given as mean ± SEM (n = 4) and are taken from Henning and Sims (*48*).

Another adult characteristic that appears during the fourth postnatal week is the occurrence of a diurnal rhythm of enzyme activity. Our results for sucrase are shown in Fig. 3. At 19 days this enzyme shows arrhythmic variation when studied ever 3 hr during a 24 hr period, whereas by day 22 a distinct rhythm with a nocturnal peak has developed. If animals are prevented from weaning, the sucrase rhythm does not appear at this time (*55*).

Here again, in relation to toxicological studies, there are two important points. Firstly that, although diet seems to have little influence on intestinal biochemistry during the suckling phase, from the weanling phase onward dietary changes may have dramatic effects on the enzymology of this tissue. Secondly that, at least from day 22 onward, significant diurnal variations may be present, thus making the timing of experiments (with respect to the light cycle) a variable that must be critically controlled.

Role of Hormones

There is now a great deal of evidence suggesting that glucocorticoids are primarily responsible for the various intestinal changes that occur in the rat and mouse at weaning (*29, 43*). Administration of glucocorticoids to suckling rats or mice causes precocious increases in the activities of sucrase (*40, 56, 57*), maltase (*56, 58*), trehalase (*56*), amino peptidase (*43, 56*), and alkaline phosphatase (*42*), as well as precocious disappearance of various lysosomal hydrolases (*59*), and the capacities for pinocytosis (*15, 19, 60*) and for the absorption of intact immunoglobulins (*19, 61*). Conversely, it has been shown that if animals are adrenalectomized during the second postnatal week, the usual decrease of pinocytosis (*62*) and increase of alkaline phosphatase (*42*) and sucrase (*63*) activities are largely prevented. On the other hand; the sucrase activity of adult rat jejunum is apparently independent of glucocorticoids, since here it is not decreased by adrenalectomy, nor increased by administration of glucocorticoids (*53*). Figure 4 shows that this adult characteristic of glucocorticoid-independence appears on day 17-18, i.e., very soon after the sucrase rise begins. Similar results have been reported for alkaline phosphatase in mouse duodenum (*42*). Thus, with respect to these two enzymes, glucocorticoids seem to be required only for the initiation of the developmental changes, not for their maintenance. The question of whether or not the pattern of glucocorticoid involvement is common to all the changes that occur in the intestinal mucosa in the third postnatal week remains to be investigated. The possibility that the intestine abruptly loses its sensitivity to certain toxic substances at this time is equally intriguing.

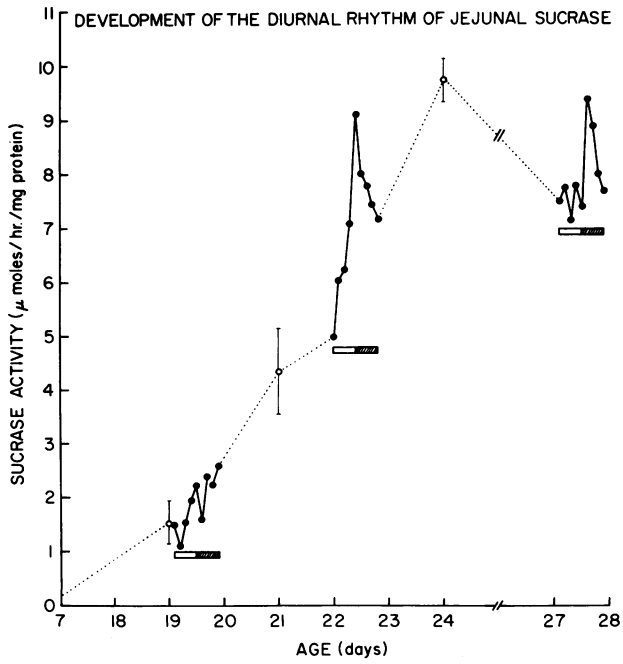

FIGURE 3. Development of the diurnal rhythm of jejunal sucrase activity: (○) the normal developmental pattern for sucrase activity measured in the morning (*54*); (●) sucrase activity measured every 3 hr beginning at 0830 hr on postnatal days 19, 22, and 27 (*55*). Open bars indicate the light period and hatched bars indicate the dark period.

In an earlier section it was pointed out that there are two possible mechanisms by which enzymic changes of the intestinal epithelium could occur: by alteration of the enzyme levels in the differentiated cells that are present on the villi, or by replacement of one population of villus cells by another which has altered enzymology. There is now considerable evidence to indicate that it is the latter method which is operative in the various postnatal changes that are observed in the rat intestine. When the distribution of sucrase along the length of the crypt-villus unit after glucocorticoid administration to 9-day-old rats was studied by cryostat sectioning of the intestine (Fig. 5), it was found that 24 hr after administration of the steroid, no sucrase activity was detectable on the villi but a very small amount was present at the mouths of the crypt. By day 11 this activity had increased and had extended along the lower halves of the villi. The process continued and by day 13 sucrase activity had reached the tips of the villi and the pattern through the whole depth of the mucosa was very similar to that for adult animals (*11*).

These results indicate that the ability of hydrocortisone to cause precocious appearance of sucrase

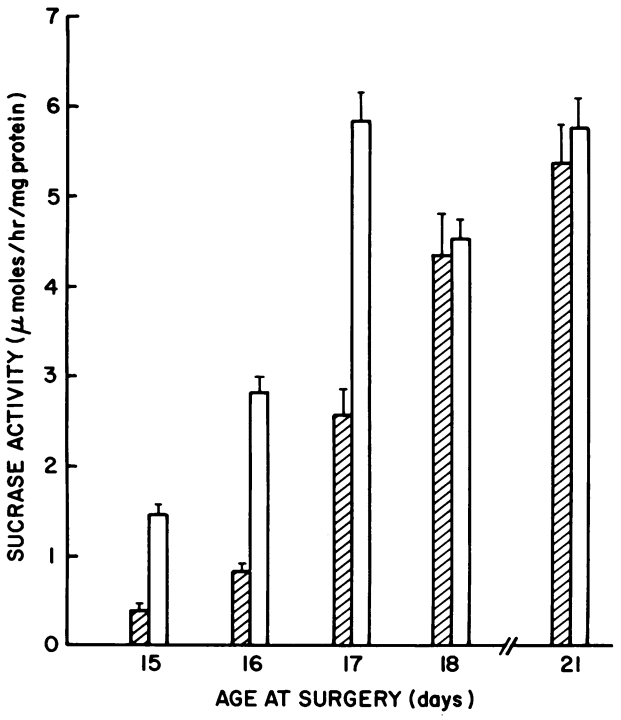

FIGURE 4. Effect of adrenalectomy on sucrase development. At each age indicated, a full litter of nine pups was used as follows: (▨) five pups were subjected to bilateral adrenalectomy; (□) four pups were sham-operated. Pups were killed 5 days after surgery and jejunal sucrase was assayed. Results are given as means ± SEM. Differences between adrenalectomized and control groups were statistically significant ($p < 0.001$) when surgery was performed on days 15, 16, and 17, but NS ($p > 0.5$) when surgery was performed on Days 18 and 21. Figure is from Henning and Sims (*48*).

is mediated via the cells of the crypt. The cells that are on the villi at the time of administration are apparently unaffected by the hormone. The rate at which the enzyme activity appeared at the base of the villi and then spread along the lengths of the villi correlated with reported migratory rates for the epithelial cells (*7, 64*).

Similar results for the pattern of sucrase appearance have been obtained by other workers both by cryostat sectioning (*64*) and by fluorescent antibody techniques (*65*). It is postulated that the same series of events occurs when endogenous glucocorticoids participate in the normal appearance of sucrase during the third postnatal week. These suggestions are supported by studies (*23, 60*) which have shown that during both the normal and the precocious loss of pinocytic capacity from the jejunum, pinocytosis does not decrease in enterocytes already present in the villi, but rather these cells are gradually replaced by new ones from the crypts that do not engage in pinocytosis.

In view of the effects of adrenalectomy and glucocorticoid administration during the suckling period, glucocorticoids have generally been regarded as being the normal cue for the developmental changes that occur in the intestine during the third and fourth postnatal weeks (*29, 34, 43*). However the problem with this supposition has been that the majority of the reported values for plasma corticosterone during development are uniformly high from the second through the third postnatal week (*66-70*). We raised the question of why the high concentrations of endogenous corticosterone did not elicit intestinal changes during the second week of life and proposed (*57, 71*) that the timing of glucocorticoid action in this system must reflect increased responsiveness of the target cells at the beginning of the third postnatal week. However, when the cytoplas-

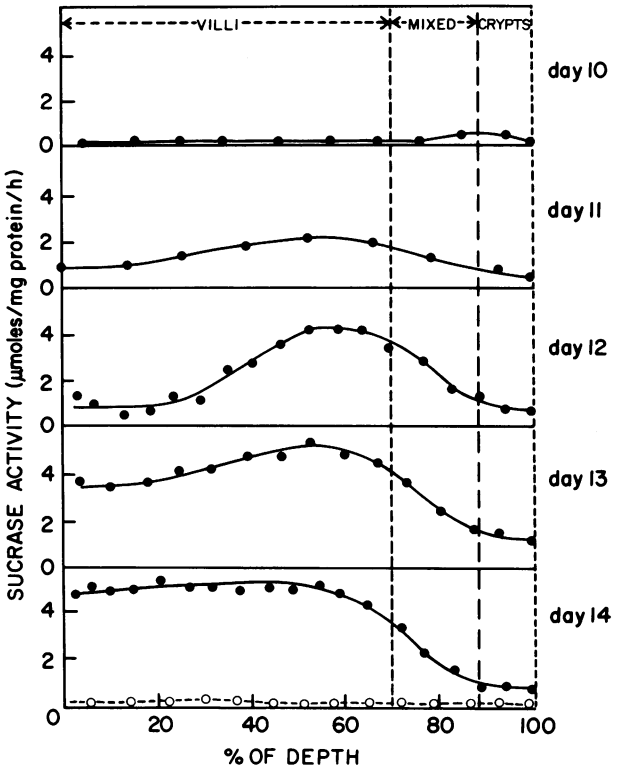

FIGURE 5. Appearance of sucrase at various cytological depths of the mucosa after administration of hydrocortisone to 9-day-old rats. A piece of jejunum was taken for cryostat sectioning and then sucrase activity was measured in homogenates prepared from sections from the various levels of the mucosa. The results for each animal are plotted against the proportional depths of the total mucosa with the top of the villi at 0% and the bottom of the crypts at 100%. The concurrent histological examinations indicated that there was not an abrupt change from pure villi to pure crypts. Sections between 70 and 90% of the total depth always contained a mixture of both villi and crypts. From Henning et al. (*57*).

mic receptors for glucocorticoids in the jejunum were assayed throughout the developmental period they were found to be present in higher concentrations during the first and second postnatal week than during the third week (*71*), thus failing to provide a basis for increasing responsiveness.

Since circulating concentrations of thyroxine are known to increase considerably between postnatal days 10 and 16 (*72-75*) we have investigated the possibility that this hormone synergizes with glucocorticoids and thereby explains the timing of the glucocorticoid-mediated changes in the intestine (*76*). The data indicate that thyroxine plays no role in the timing of the developmental appearance of sucrase activity, although it does have an important permissive effect in determining the slope of the developmental rise of sucrase activity.

Before pursuing other factors which might account for the timing of endogenous glucocorticoid action on the small intestine during development, we decided to re-examine the ontogeny of plasma corticosterone (*54*). All previous developmental studies of this hormone had measured its total plasma concentration. However, a large proportion of the total is bound to plasma transcortin and only the free fraction is biologically active (*77, 78*). When the developmental pattern of free corticosterone is plotted together with sucrase and lactase activities of the same animals (Fig. 6) it can be seen that the hormone concentration begins to rise approximately two days before the enzymic changes begin. In view of earlier demonstrations (*57, 64*) that glucocorticoid effects are mediated by the crypt cells but are not detected until those cells leave the crypts and migrate out the villi, the timing of the surge of free corticosterone (Fig. 6) strongly suggests that it initiates the enzymic changes that occur in the small intestine during the third and fourth postnatal weeks.

An important corollary of these studies with plasma corticosterone is that stress may elicit significant changes in intestinal biochemistry during the developmental period. Although the hypothalamus-pituitary-adrenal axis is quiescent from day 3 through day 10 (*67, 68, 70*), between days 11 and 18, stress-induced elevation of plasma corticosterone can be expected to cause precocious maturation of intestinal function. The stress effect of administering nutrient by gastrostomy has already been mentioned (*41*). More recently, it has been shown that the effects of premature weaning are in fact due to the adrenal stress response to starvation (*79*). The stress effects of drugs, surgery and sickness during the developmental period have not been systematically studied, but would be certainly predicted to cause precocious maturation of the small intestine.

In summary, the first month of postnatal development in the rat is characterized by marked changes in intestinal biochemistry. The gluococorticoid hormones and the thyroid hormones have important influences on these changes. In the case of the glucocorticoids there is a relatively short period during which they are active: namely, between day 14, when the rise of available hormone begins, and day 17-18, when tissue sensitivity to these steroids is lost. This pattern, together with the demonstration that glucocorticoids act selectively on crypt (as opposed to villus) epithelial cells, may have important implications for toxicological studies of the intestine. Likewise the appearance of diurnal rhythms and dietary dependence of digestive enzymes during the fourth postnatal week are useful pointers for controls that must be considered in investigations of the interactions of toxic substances with intestinal tissue.

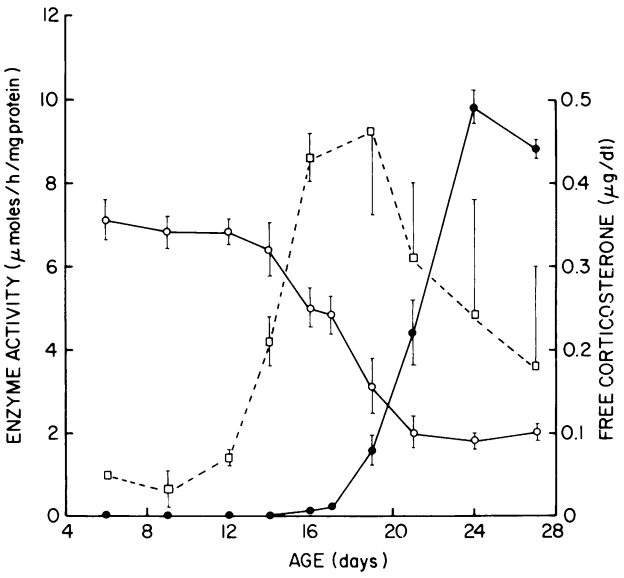

FIGURE 6. Developmental patterns for the activities of the enzymes lactase and sucrase in jejunal mucosa as compared with free corticosterone in plasma: (○) lactase activity; (●) sucrase activity; (□) free corticosterone. Values are given as mean ± SE (n = 5). Absence of error bars indicates that the SE was smaller than the symbol. From Henning (*54*).

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